REMARKS

Claims 6, 9 and 10 have been amended. Claims 1-4 and 14-16 have been cancelled. Accordingly, Claims 5-13 and 17-20 are pending for examination.

Utility

Claims 5-13, and 17-20 were rejected under 35 U.S.C. 101 on the assertion that the claimed invention is not supported by either a specific asserted utility or a well established utility. The Examiner asserts that the specification fails to correlate the amount of claimed encoded polypeptide necessary that would predictably provide any sort of therapeutic benefit. For example, the Examiner asserts that the specification designates some of the PRO polypeptides as "positive" because there was a "higher" amount of TNF-α in the PRO polypeptide treated samples compared to the negative control samples. However, according to the Examiner, it is not clear how this higher amount of TNF-α translates into any significant biological value. For example, the Examiner questions how the higher value compares to the normal physiological serum levels of the cytokine.

The accompanying Declaration of Dr. Paul Godowski describes the methodology utilized in the experiments of Example 17 in which the polypeptides encoded by the claimed polynucleotides were shown to enhance TNF-α levels. As stated in the accompanying Declaration, polypeptides which were reported as positive in the TNF-α assay of Example 17 stimulated the release of at least 50-fold and up to more than 300-fold more TNF-α than the control samples. As the experiments were conducted on human blood, the results demonstrate that the claimed polypeptides were able to increase the level of TNF-α to a level at least 50-fold greater than the amount normally present in human blood. In fact, as stated in the accompanying Declaration, because TNF-α is present at an undetectable level in human blood, the foregoing levels of enhancement are relative to the minimal amount of TNF-α detectable under the assay conditions utilized. Accordingly, Applicants maintain that the results of these experiments are biologically significant.

The Examiner also asserts that Goeddel et al. (previously submitted as Exhibit D) teaches (page 602) that increases in TNF-α can both inhibit the growth of cells and/or stimulate the growth of cells. Thus, according to the Examiner, any proposed therapeutic benefit to increasing

serum levels of TNF-α in order to treat tumors is non-specific and speculative at best because there are many different types of tumor cells and each type may respond in different ways to increased concentrations of TNF-α. The Examiner asserts that this includes stimulating the growth of cancer cells. According to the Examiner, Goeddel et al. also teach (page 600, 1st column) that the expression of TNF-α is "transient" even in the presence of continuous mitogenic stimuli. Thus, according to the Examiner, even though the specification asserts that the polypeptide was "positive" in the assay, the prior art teaches that any corresponding increases in TNF-α are fleeting.

Applicants maintain that the fact that different cell types respond to TNF-α in different ways does not deprive the claimed polypeptides of utility. The utility requirement only mandates that the polypeptides encoded by the claimed polynucleotides have beneficial activity with respect to at least one cell type. Table 3 of Goeddel indicates that TNF-α reduced proliferation of many cell lines, including cell lines derived from breast carcinoma, sarcoma, cervical carcinoma, melanoma, ovarian carcinoma, fibrosarcoma and carcinoma. The fact that other cell types may not beneficially respond to TNF-α does not detract from the utility of the claimed polypeptides in treating cancer resulting from the growth of those cancer cells whose proliferation is inhibited by the claimed polypeptides.

Furthermore, Applicants maintain that the references in addition to Goeddel (Exhibits B, C, and E-N) which were provided along with the Declaration of Dr. Paul Godowski in response to the previous Office Action further demonstrate that enhanced TNF-α levels are beneficial in treating certain conditions, such as cancer and viral infection and in reducing the deleterious effects of ionizing radiation. Applicants maintain that the beneficial effects described in these references further support the utility of the claimed polynucleotides.

With respect to the Examiner's assertion that Goeddel indicates that TNF-α expression is "transient" even in the presence of continuous mitogenic stimuli, Applicants first note that this observation was in the context of stimulation of murine macrophage PU5-1.8 cells with PMA. As stated in the accompanying Declaration, one cannot extend the transient induction of TNF-α production by murine macrophage PU5-1.8 cells upon contact with PMA observed in Goeddel, D.V. et al. Cold Spring Harbor Symposia on Quantitative Biology 51:597-609 (1986) to infer that the polypeptides encoded by the claimed polynucleotides will necessarily induce transient

production of TNF-α in human cells. In addition, as stated in the accompanying Declaration, in an *in vitro* analysis such as that conducted by Goeddel et al., all the cells are simultaneously contacted with the agent which enhances TNF-α production, thereby permitting any regulatory consequences of continuous stimulation to occur. Such *in vitro* assays are not comparable to *in vivo* therapy in which different groups of cells are periodically exposed to the stimulatory agent over time. Because different groups of cells will come in contact with the stimulatory agent over time, TNF-α production will be continuously stimulated in the therapeutic context. Accordingly, the transient expression of TNF-α observed upon continuous stimulation is not relevant to and does not detract from the therapeutic usefulness of the claimed polynucleotides.

Furthermore, as stated in the accompanying Declaration, in addition to the benefits of increasing TNF-α levels for treating certain conditions, other conditions, such as rheumatoid arthritis and Crohn's disease, may be treated by reducing TNF-α levels. For example, the drug Enbrel is a fusion between TNF-α receptors and an immunoglobulin which is used to treat rheumatoid arthritis by reducing TNF-α levels. Inhibition of polypeptides which enhance TNF-α production, such as the polypeptides encoded by the polynucleotides claimed in the present application, is useful for treating such conditions. Accordingly, the polypeptides encoded by the claimed polynucleotides are useful targets for treating diseases resulting from elevated TNF-α levels.

In addition, Applicants note that the M.P.E.P. states that "Courts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. § 2107.01, part III (8th ed. 2004) (emphasis added). In addition, the Courts have held that "the test results need not absolutely prove that the compound is pharmacologically active. All that is required is that the tests be '*reasonably* indicative of the desired [pharmacological] response.'" *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, italics in original). Clearly, the stimulation of TNF-α release meets the test of "mere identification of a pharmacological activity" set forth in the M.P.E.P.

The Examiner also asserts that the prior art indicates that TNF-α is highly toxic. Hallahan et al. is cited as teaching that while TNF-α enhances direct tumor cell killing, it was noted that

increased serum concentrations of TNF-α contributed to systemic toxicity and limited the therapeutic efficacy. Applicants maintain that many therapeutically valuable substances are toxic at elevated levels or even at the levels present during therapy. In particular, traditional chemotherapy drugs are systemically toxic, but their beneficial effects on the tumor outweigh any potential negative effects on normal cells.

In addition, Applicants note that for pharmaceutical inventions, usefulness in patent law does not require a demonstration of safety and efficacy in humans. (*See In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). In fact, it is well-established that it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness of a compound. MPEP 2107.03V; *see also In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981).

The Examiner asserts that the specification only proposes that PRO polypeptides testing positive in this assay are useful for "research purposes" and for therapeutic treatment where enhanced TNF-α release would be beneficial. The Examiner maintains that the instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 US.P.Q. 689 (S. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility.

Applicants maintain that, in contrast to the situation in *Brenner v. Manson*, where no characterization of the pharmaceutical properties of the claimed compounds had been performed, Applicants have demonstrated that the polypeptides encoded by the claimed polynucleotides enhance TNF-α levels by at least 50-fold. Furthermore, Applicants note that, as stated in *In re Brana*, "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby

eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer." (*See In re Brana*, 34 U.S.P.Q.2d 1443 (Fed. Cir. 1995). Accordingly, Applicants maintain that they have demonstrated sufficient therapeutic utility for the claimed polynucleotides to satisfy the utility requirement.

Enablement

Claims 5-13, and 17-20 remain rejected under 35 U.S.C. 112, first paragraph. The Examiner asserts that, because the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants maintain that, for the reasons presented above, the claimed polynucleotides possess a substantial, specific and credible utility. Accordingly, Applicants submit that one skilled in the art would know how to use the claimed polynucleotides.

New Rejections:

Claims 6 and 9-10 were rejected under 35 USC 112, first paragraph on the assertion that the specification does not contain a written description of the claimed invention. According to the Examiner, the limitation of an extracellular domain comprising amino acids 17-234 of SEQ ID NO:6 has no clear support in the specification and the claims as originally filed.

Applicants have deleted the terminology "extracellular domain" from the claims. Applicants maintain that Figure 6 discloses the presence of a signal peptide between amino acids 1-16 of the polypeptide of SEQ ID NO: 6, which is encoded by the polynucleotide of SEQ ID NO: 5, and the presence of a transmembrane domain between amino acids 235-254 of SEQ ID NO: 5. The demarcation of these regions of the protein also demarcates the amino acids at positions 17-234 of SEQ ID NO: 6. Accordingly, the recitation of amino acids 17-234 of the polypeptide of SEQ ID NO: 6 does not constitute new matter.

Element (d) of Claim 6 and Claim 10 have been amended to recite that the polynucleotides claimed therein do not encode amino acids 1-16 of SEQ ID NO: 6. As noted above, Figure 6 indicates that the polypeptide of SEQ ID NO: 6 has a signal peptide located between amino acids 1-16. Accordingly, the reference to this portion of the polypeptide of SEQ ID NO: 6 does not constitute new matter.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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